REMARKS

Following entry of the above amendment, claims 1-3, 5-7, 11, and 25-40 will be pending in this application, new claims 27-40 having been added. Support for new claims 27-40 can be found throughout the specification as filed, e.g., at paragraph [0056].[1] No new matter has been added.

35 USC § 112, first paragraph

Claims 1-3, 5-7, 11, 25, and 26 were rejected as allegedly not enabled for the full scope of the claims. The Office action states (at pages 2-3):

> [T]he specification, while being enabling for a method for treating a glioma in a mammal, the method comprising: (a) administering at least one vaccination of dendritic cells ("DC") to said mammal suffering from a glioma, **wherein said DC are autologous and primed *ex vivo* with autologous glioma cells**; and (b) after glioma recurrence following (a), administering a regimen of chemotherapy to said mammal, wherein said regimen of chemotherapy includes the administration of at least one chemotherapeutic agent selected from the group consisting of temozolomide, procarbazine, vincristine, BCNU, CCNU, thalidomide, irinotecan, isotretinoin, imatinib, etoposide, and combinations thereof, does not reasonably provide enablement for said method comprising *administering any DC, DC that are not primed, or that are primed with any unknown source*. (emphasis in original)

Applicants respectfully traverse the rejection in its entirety.

Primed versus unprimed dendritic cells

At page 4, the Office action states that "the specification does not provide guidance or examples for treating glioma in patients comprising administering **DCs that are not primed**" (emphasis in original). However, this is not the case. For example, the application teaches at paragraphs [0034], [0035], and [0038] that unprimed dendritic cells may be used in the disclosed methods. Paragraph [0035], in particular, provides the guidance: "in various embodiments of the present invention, DC may be delivered directly into a tumor bed or tumor region without first

[1] Paragraph numbers refer to the published version of the present application, US 2007/0020297.

being primed ex vivo; the DC process the tumor antigens in vivo." Additionally, the application incorporates by reference US 2004/0057935.[2] This publication provides working examples of prolongation of survival of animals with new and established tumors by administration of unprimed dendritic cells intracranially (see Examples 4 and 5). Therefore, applicants submit that the application provides sufficient guidance for use of unprimed dendritic cells in the claimed methods.

At pages 4-5, the Office action cites Okada et al., 1998, Int. J. Cancer, 78:196-201 ("Okada"), Liau et al., 1999, J. Neurosurg., 90:1115-24 ("Liau") and Heimberger et al., 2000, J. Neuroimmunol., 103:16-25 ("Heimberger") for the proposition that "unprimed or unpulsed DCs are ineffective for treating tumors." Contrary to the publications cited by the Office, Ehtesham et al., 2003, J. Immunother., 26:107-116 ("Ehtesham"; submitted herewith) discloses that unprimed dendritic cells were effective to inhibit tumor growth and prolong survival of animals with gliomas when administered intratumorally (see Figs. 2-3). The vaccinated animals were characterized by intratumoral T-cell infiltration and tumor-specific CTL activity (see Figs. 5-6). The publications cited by the Office all utilized peripheral or systemic methods of dendritic cell administration, rather than intratumoral administration as disclosed in Ehtesham. Okada describes intravenous dendritic cell administration; Liau describes subcutaneous dendritic cell administration; and Heimberger describes intraperitoneal dendritic cell administration. One of ordinary skill would recognize based on the state of the art at the time of filing and the guidance and examples provided in the present application that either unprimed or primed dendritic cells could be used in the claimed methods and would be able to tailor the means of administration based on the priming state of the dendritic cells, if necessary. Therefore, undue experimentation would not be needed to practice the claimed methods using unprimed dendritic cells.

Source of dendritic cell priming

At pages 5-6, the Office action states that "one of skill in the art could not predictably treat glioma in a patient with DCs primed *ex vivo* with any unknown antigen or source, other

[2] The incorporation by reference is completed above by amending the specification to refer to the publication of U.S. patent application Ser. No. 10/251,148.

than primed with the patient's autologous glioma cells that express the antigens required to be targeted by the DCs." Applicants respectfully disagree. As discussed above, even unprimed dendritic cells can be used in the claimed methods. Applicants submit that if the dendritic cells are to be primed *ex vivo*, sources of antigen other than the patient's autologous dendritic cells can also be used. The present application contemplates that a "a host of methodologies" for preparing dendritic cells could be used (see paragraph [0010]). For example, dendritic cells can be primed by numerous methods, e.g., with tumor associated antigens as peptides, proteins, tumor cell lysates or eluates, DNA, RNA, or expressed by viral or non-viral vectors transfected into dendritic cells (see Melcher et al., 2002, Clin. Oncol. (R. Coll. Radiol.) 14:185-192; submitted herewith ("Loading DC with antigen for anti-tumor immune activation, pages 188-190)). Okada discloses the use of dendritic cells pulsed with a synthetic peptide ($E7_{49-57}$) expressed on the tumor cells (abstract). This treatment was effective in 67% of animals treated, whereas treatment with a control influenza peptide not expressed on the tumor cells was not effective (abstract).

Liu et al., 2003, Cancer Control, 10:138-147 (submitted herewith) discloses that several tumor-associated antigens shared by gliomas have been identified, such as tenascin, gp240, EGFRvIII, tyrosinase, TRP-1, TRP-2, gp100, MAGE-1, and MAGE-3 (page 140). Liu et al., 2003, J. Immunother., 26:301-312 (already of record) observed an immune response against a TRP-2 peptide, and this response was also found to induce chemosensitivity of gliomas in methods similar to those claimed (see Liu et al., 2005, Oncogene, 24:5226-34; already of record). Parmiani et al., 2002, J. Natl. Cancer Inst., 94:805-818 (submitted herewith) describes phase I and II clinical trials using tumor associated antigen peptides (including gp100, tyrosinase, and MAGE-3) in which patients exhibited a response to the treatment (see Table 4), indicating that peptides can be a viable source of antigen for dendritic cell therapy. The post-filing date reference, Zhang et al., 2007, Clin. Cancer Res., 13:566-575, discloses several additional antigens associated with gliomas, most of which appear to be expressed in the majority of tumors (see Table 3). Casey et al., 2003, Immunology, 110:105-111 (submitted

herewith) discloses that a protein isolated from a non-autologous tumor can be used in a dendritic cell vaccine.

It is apparent that several sources of antigen for use in priming dendritic cells were known by applicants' filing date. The selection of a source of antigen for priming (or not priming) was within the skill of the ordinary practitioner at the time of filing, and undue experimentation would not have been necessary to practice the full scope of the claims using unprimed dendritic cells or dendritic cells primed *ex vivo*.

Allogeneic dendritic cells

At page 6, the Office action states that "[g]iven the teaching of the art, one of skill in the art could not predictably treat glioma in a mammal comprising administering any DCs other than autologous DCs." The Office cites Merrick et al., 2008, Cancer Immunol. Immunother., 57:897-906 ("Merrick"), as allegedly "disclosing that autologous DCs provide significantly better protection against tumors than 'semi-allogeneic' DCs (Figure 3)." However, Merrick also discloses that in some applications, such as intratumoral injection of dendritic cells or the use of tumor cell/dendritic cell hybrids, semi-allogeneic dendritic cells are more potent for immunotherapy (see page 905, left column). Merrick suggests that in such applications, "allogeneic DC are a reasonable and practical source of APC for clinical use" (page 898, right column). The present application clearly discloses intratumoral injection of dendritic cells as one possible mode of administration (see, e.g., paragraphs [0035] and [0037]). Therefore, Merrick does not provide evidence that the specification does not provide enablement for use of non-autologous dendritic cells.

Based on the above arguments and evidence, applicants submit that the claims are fully enabled. One of ordinary skill would have recognized that numerous methods of preparing and administering dendritic cells were available at the time of the filing of the application that could have been utilized in the claimed methods without undue experimentation. Applicants therefore request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants submit that the pending claims are allowable and request early and favorable action thereon. Applicants do not concede any positions of the Office that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

If it would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 617-521-7020.

This reply is being submitted with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 22862-0004US1.

Respectfully submitted,

Date: June 4, 2010

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